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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,388	11/07/2005	Sun Lee	20050-00004	2704

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JHK Law
P O Box 1078
La Canada, CA 91012-1078

EXAMINER	
WORLEY, CATHY KINGDON	
ART UNIT	PAPER NUMBER
1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,388	LEE ET AL.	
	Examiner	Art Unit	
	CATHY K. WORLEY	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed April 29, 2008, has been entered.

2. Claims 1-8 are pending and are examined in this Office Action.

3. The text of those sections of Title 35, U.S. Code not included in this office action can be found in a prior office action.

Rejections and Objections that are Withdrawn

4. The objections to claims 1, 3, 4, 7, and 8 are withdrawn in light of the Applicant's amendments to the claims.

Claim Objections

5. Claim 5 remains objected to because of the following informalities: the recitation of "the C-terminal or N-terminal of said EGF" is grammatically incorrect. The Applicant is advised to replace this recitation with - - the C-terminus or N-terminus of said EGF - - , or alternatively with - - the C-terminal end or N-terminal end of said EGF - - .

The Applicant states that claim 5 was clarified to feature C-terminal and N-terminal ends (see first paragraph on page 4 of the response filed on April 29, 2008);

however, this amendment was not made in the amended claims submitted on April 29, 2008.

Appropriate correction is requested.

Claim Rejections - 35 USC § 103

6. Claims 1, 2, 4-6, and 8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hooker et al (WO 98/21348, published on May 22, 1998) in view of Rosen et al (WO 01/79442, published on Oct. 25, 2001), and further in view of Simons et al (US Patent 5,716,802, issued on Feb. 10, 1998) for the reasons of record stated in the previous Office Action mailed on Oct. 29, 2007. The Applicant's arguments in the papers filed on April 29, 2008, were fully considered but were not found to be persuasive.

The claims are drawn to methods of producing fusion proteins comprising epidermal growth factor (EGF) and human serum albumin (HSA) in transgenic plants.

The instant claims are obvious over the prior art because there was some teaching, suggestion, or motivation in the knowledge generally available to one of ordinary skill in the art to combine the reference teachings, and there was a reasonable expectation of success in combining the teachings.

SCOPE AND CONTENT OF THE PRIOR ART – PRIMARY REFERENCE

Hooker et al teach the production of EGF in plants (see entire document). Hooker et al suggest that the EGF can be produced as a fusion with a protein that is efficiently produced in plants systems (see page 6, lines 9-11; and abstract). They teach production in *Nicotine abacus* (see page 5, line 25), and also teach that any plant from the plant kingdom may be utilized (see page 7, line 20). Hooker et al teach that a method for producing EGF in a plant comprises the steps of sub cloning the coding sequence into a plant expression vector, transferring the vector to *Agrobacterium*, culturing leaf disks or suspension cells with *Agrobacterium*, selecting for transform ants, permitting growth of plant cells into whole plants, and extracting the growth factor (see page 8, lines 16-29). They teach that the plant expression vector should comprise a promoter and a terminator (see page 9, lines 5-8).

DIFFERENCES BETWEEN THE CLAIMED INVENTION AND THE TEACHINGS OF HOOKER et al.

Hooker et al do not teach expression of EGF as a fusion with HSA. They do not teach N-terminal or C-terminal fusions with HSA, nor do they teach stability of said fusions.

SCOPE AND CONTENT OF THE PRIOR ART – SECONDARY REFERENCE

Rosen et al teach expression albumin fusion proteins (see entire document). They teach that therapeutic proteins, such as growth hormones, are typically labile molecules exhibiting short shelf-lives (see page 2, lines 6-7). They teach that therapeutic proteins can be stabilized to extend the shelf-life and/or to retain the

therapeutic protein's activity by fusing the therapeutic protein to albumin (see page 2, lines 24-27). Rosen et al teach that the HSA may be fused to either the C-terminus or the N-terminus of the therapeutic protein (see paragraph bridging pages 115-116).

SCOPE AND CONTENT OF THE PRIOR ART – TERTIARY REFERENCE

Simons et al teach the production of recombinant HSA in transgenic plants (see column 3, lines 41-46 and Figure 1).

LEVEL OF ORDINARY SKILL IN THE PERTINANT ART

The pertinent art is the field of molecular biology and biochemistry, and one of ordinary skill in this art would have earned a Ph.D. in molecular biology, biochemistry, plant biology, or some other related field. One of ordinary skill in this art would have been well-versed in techniques for heterogonous expression of recombinant proteins and would be familiar with the literature encompassing production of fusion proteins and production of therapeutic proteins in plants. This skill level is evidenced by the skill of Hooker, Rosen, Simons, and their co-authors.

FINDING OF OBVIOUSNESS

At the time the invention was made, it would have been obvious and within the scope of one of ordinary skill in the art to modify the method taught by Hooker et al to produce fusion proteins as taught by Rosen et al. These teachings include each element recited in the instant claims. Because Rosen et al teach that fusing therapeutic proteins to HSA can increase the shelf-life and retain the biological

activity of the therapeutic protein, one of ordinary skill in the art would have been motivated to modify the method taught by Hooker et al to produce EGF-HSA or HSA-EGF fusion proteins to arrive at the instant invention. Because of the success in producing EGF in plants taught by Hooker et al, and the success in producing HSA in plants taught by Simons et al, and the success in producing stable, biologically active fusion proteins taught by Rosen et al; one would have an expectation of success in producing HSA-EGF or EGF-HSA fusion proteins in plants, and one would have predicted that such fusion proteins would have enhanced stability compared to EGF expressed as a non-fusion protein. For these reasons, the instant claims are obvious over the prior art.

APPLICANT'S ARGUMENTS

The Applicant argues that one would not have had a reasonable expectation of success in combining the references because the purpose of the fusion protein in Rosen and Simons is a different purpose; one for efficiency of production and one for stability (see second paragraph on page 5 of the response). This is not persuasive, however, because efficiency of production and stability of the product are closely related because a product that is more stable will accumulate to higher levels due to reduced proteolysis/degradation. Furthermore, the fact that there was a different purpose does not provide any evidence or reason why the production of an HSA-EGF fusion in a plant would not succeed. Given the success taught by Hooker et al of producing EGF in a plant, and the suggestion of producing it as a fusion protein,

and given the success of Simons et al in producing HSA in a plant, and given the success of Rosen of producing HSA fusions with small therapeutic proteins; one would have had a reasonable expectation of success in combining the references to produce an HSA-EGF fusion in a plant.

The Applicant further argues that Rosen teaches a method to excrete through plant cells plasma membrane recombinant proteins utilizing plant signal peptides and this method is quite different from the instant invention (see third paragraph on page 5 of the response). This is not persuasive, however, because there is nothing in the instant claims to exclude the use of a signal peptide for secretion. Therefore, the applicant is arguing a limitation that is not in the claims.

The Applicant further argues that Rosen teach the use of anti-HSA agars to purify the products which is expensive and impractical and therefore one would not turn to this method (see third paragraph on page 5 of the response). This is not persuasive, however, because Rosen teach that their method provides a way to make small therapeutic proteins with an increased shelf-life, and this is a desirable characteristic for a therapeutic protein, such as EGF, therefore, one would have been motivated to utilize the method taught by Rosen in order to make a product with an increased shelf-life.

7. After further consideration and in light of the ruling in *KSR*, 82 USPQ2d at 1396, claims 3 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Hooker et al (WO 98/21348, published on May 22, 1998) in view of Rosen et al (WO 01/79442, published on Oct. 25, 2001), and further in view of Simons et al (US Patent 5,716,802, issued on Feb. 10, 1998).

The claims are drawn to methods of producing fusion proteins comprising epidermal growth factor (EGF) and human serum albumin (HSA) in transgenic plants, including wherein the nucleic acid sequence encoding EGF comprises nucleotides 1-159 of SEQ ID NO:1.

As discussed above, methods of producing fusion proteins comprising EGF and HSA in transgenic plants are obvious over Hooker et al in view of Rosen et al and further in view of Simons et al. The additional limitation that the nucleic acid encoding EGF comprises nucleotides 1-159 of SEQ ID NO:1 is not sufficient to overcome this obviousness. It was well-known in the art at the time of filing that different codons can be utilized to encode the same protein due to the degeneracy of the genetic code; and making nucleotides substitutions that do not change the amino acid sequence of the encoded protein was well known in the art at the time of filing. Therefore, any nucleic acid that encodes the same protein as another nucleic acid is an obvious variant unless there is evidence of an unexpected advantage to the particular substitutions made. In the instant case, the specification teaches that SEQ ID NO:1 was modified to have codon usage suitable for expression in either a bacterium or a plant cell and therefore is significantly advantageous in expression in a plant cell (see lines 10-15 on page 7 of the specification). However,

codon-optimization for a particular host system was known in the art at the time of filing, and there are no data presented to demonstrate that the particular results achieved with SEQ ID NO:1 were better than would have been expected with any other codon-optimized sequence. Therefore, claims 3 and 7 are unpatentable for being obvious over the prior art of record.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cathy K. Worley whose telephone number is (571) 272-8784. The examiner is on a variable schedule but can normally be

reached on M-F 10:00 - 4:00 with additional variable hours before 10:00 and after 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Cathy K. Worley/
Patent Examiner, Art Unit 1638